IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Amar Lulla, *et al.*	§	
		§	Group Art Unit: 1616
Serial No.:	10/518,016	§	
		§	Examiner: Kristie Latrice Brooks
Filed:	July 6, 2005	§	
		§	Confirmation No.: 4912
For:	COMBINATION OF AZELASTINE AND STEROIDS	§	
		§	

DECLARATION UNDER 37 CFR § 1.132

I, Geena Malhotra, hereby declare and say that:

1. I am a co-inventor of the invention claimed in the above-identified patent application.

2. Attached as Exhibit A is comparison data for five compositions:

   Column 1: Azelastine.HCl
   Column 2: Budesonide
   Column 3: Azelastine.HCl & Budesonide
   Column 4: Fluticasone Propionate
   Column 5: Azelastine.HCl and Fluticasone Propionate

Table I of Exhibit A sets for the ingredient list for the five compositions. Table II of Exhibit A sets forth comparative stability data for the five compositions. The results in Table II show the impurity levels in the initial compositions, and after storage under certain conditions: for example "25/60 RH at 1 M" means the composition was stored for one month at a temperature of 25 degrees C and at a relative humidity of 60. The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone

propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

3. Attached as Exhibit B is a compilation of statements from 6 medical practitioners, labeled B1-B6, along with typed transcriptions. As is self-evident, these statements attest to various advantages and superior results associated with patient use of the DUONASE product comprising azelastine and fluticasone.

4. A pharmaceutical formulation comprising azelastine and fluticasonse is commercially available where approved as DUONASE nasal spray, as shown in attached Exhibit C containing information from the following website:
http://www.cipladoc.com/therapeutic/admin.php?mode=prod&action=disp&id=213.

5. Attached as Exhibit D are descriptions of the testing method used to generate the stability data discussed in Exhibit A. Exhibit D also states the nature of the impurities observed in the compositions described in Exhibit A and how those impurities were detected.

6. Based on my analysis of the entirety of data provided in the Exhibit A, I have concluded that the azelastine and fluticasone composition displays an unexpectedly beneficial stability when compared to the azelastine and budesonide composition.

7. I am unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid.

8. The present application is licensed to Meda Pharmaceuticals.

9. I, Geena Malhotra, further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: September 23, 2010

Geena Malhotra

EXHIBIT A

Comparative Composition data of Azelastine with steroids

Ingredients	**Azelastine (%w/~~w~~v)**	**Budesonide (%w/w)**	**Azelastine + Budesonide (%w/w)**	**Fluticasone (%w/w)**	**Azelastine + Fluticasone (%w/~~w~~v)**
Drugs	137 mcg	64 mcg	137 + 64 mcg	50 mcg	140 + 50 mcg
MCC+CMC (Avicel RC)	–	-	2.0	~~0.75~~1.5	~~2.0~~1.5
HPMC	0.10	-	-	-	-
Dispersible cellulose	-	1.25	-	-	-
Dextrose Anhy.	-	-	-	~~2.5~~5.0	-
Anhy. Glucose	-	5.0	-	-	-
Glycerin	-	-	2.3	-	~~2.3~~2.6
Polysorbate 80	-	0.016	0.005	0.~~0025~~005	0.~~005~~025
BKC ~~10% w/v solution~~ NF	0.0125	-	0.005	~~100 ml~~0.02	0.1~~0~~
Phenyl ethyl alcohol	-	-	-	0.~~1~~25	0.25
Pot sorbate	-	0.12	-	-	-
Disodium EDTA	0.05	0.01	0.01	-	~~0.01~~
Sodium Chloride	0.68	-	-	-	-
Citrate Monohydrate	0.048	-	-	-	-
Disodium Phosphate	0.322	-	-	-	-
Hydrochloric acid	-	q.s.	-	-	-

Comparative Stability data of Azelastine with steroid Compositions

Stability tests	Azelastine	Budesonide	Azelastine + Budesonide	Fluticasone	Azelastine + Fluticasone
	INITIAL	**INITIAL**	**INITIAL**	**INITIAL**	**INITIAL**
Assay	100	97.6	98+97	101.6	100+101.12
PH	6.78	4.51	6.0	6.4	6.1
Total Impurity	0.03	0.26	<0.1 +2.32 ~~+0.11~~	0.52	0.08+ 0.6
	25/60 RH at 1M	**25/60 RH at 1M**	**25/60 RH at 1M**	**25/60 RH at 1M**	**25/60 RH at 1M**
PH	6.86	4.68	5.94	Not Done	Not Done
Total Impurity	0.12	0.25	<0.1+ 0.97 ~~+0.07~~	Not Done	Not Done
	25/60 RH at 3 M	**25/60 RH at ~~3M~~ 2M**	**25/60 RH at 3 M**	**25/60 RH at 3 M**	**30/65 RH at ~~1M~~ 3M**
PH	6.76	4.6	5.96	6.21	5.85
Total Impurity	0.13	0.42	<0.1+5.39 ~~+0.16~~	0.46	0.2+0.84
	40/75 RH at 1M	**40/75 RH at 1M**	**40/75 RH at 1M**	**40/75 RH at 1M**	**40/75 RH at 1M**
PH	6.86	4.69	5.92	6.35	5.82
Total Impurity	0.13	0.29	<0.1+5.53 ~~+0.05~~	0.52	0.4+0.89
	40/75 RH at 3M	**40/75 RH at ~~3M~~ 2M**	**40/75 RH at 3M**	**40/75 RH at 3M**	**40/75 RH at 3M**
PH	6.76	4.61	5.91	5.98	5.81
Total Impurity	0.18	0.49	<0.1+18.29 ~~+0.23~~	0.53	0.37+0.85

Exhibit B1

Dr. C. M. Mathew Chooracken
B. Sc., M. B. B. S., M. S. (E. N. T.) D. L. O.
Senior Specialist in E.N.T.
Civil Surgeon
District Hospital, Kottayam
Reg. No. 9473

Consultation:
Behind Margin Free Market
Near Kottayam East Police Station
Collectorate P.O., Kottayam - 686 002
Ph: 2564884, Mb: 9447288822

To Cipla Respiratory L

I have been using the Duonase nasal spray regularly for my nasal allergy patients. I found it very effective when compared to the available other nasal sprays. Oral medication can be avoided as well.

Kottayam
23/8/05

Dr. C. M. Mathew Chooracken
B. Sc., M. B. B. S., M. S. (E. N. T.) D. L. O.
Senior Specialist in E. N. T.
Civil Surgeon,
District Hospital, Kottayam
Reg. No. 9473

Dr. C.M.MATHEW CHOORACKEN

To Cipla Respiratory

I have been using the Duonase nasal spray regularly for my nasal allergic patients. I found it is very effective when compared the available other nasal sprays. Oral medication can be avoided as well.

Kottayam
23/8/05

Confidential

डॉ. पी.एन. लेजनकर
एम. एस. (ई.एन.टी.)
नाक, कान, गला एवं गर्दन रोग विशेषज्ञ
पूर्व रजिस्ट्रार ई.एन.टी. हॉस्पिटल, बाम्बे

क्लिनिक
गुजराती समाज, नई सड़क, उज्जैन ☎ 2561981
समय प्रातः 11 से 2.00
जय मेडिकल सेन्टर (चरावड़ा पेट्रोल पम्प के पास) घंटाघर, फ्रीगंज, उज्जैन ☎ 2514884
समय सायं 6 से 8.30
रविवार अवकाश

विशेषज्ञ
- नाक एवं सायनस इन्डोस्कोपी (दूरबीन द्वारा आपरेशन) • माइक्रोलेरिन्जियल सर्जरी
- माइक्रोइयर सर्जरी (जर्मनी, फ्रांस एवं स्वीटजरलेण्ड से प्रशिक्षण प्राप्त) • नाक की प्लास्टिक सर्जरी (राईनोप्लास्टी)

18.8.08

Regarding Duonase

Using this product for last so many days.
This is ideal, first line agent for the patient. The combination is adequate to deal with all types of allergy.
- Acts on both phases (early and late phase of allergy i.e. inhibits)
- Antagonise the H1 receptor activity & few side effects.
- Acts on multiple receptors.

The systemic bioavailability is less so can be used for a longer period without side effects.

Tough to allergy Safe to [illegible]

[signature]

DR.P.N.TEJANKAR

M.S. (E.N.T)
E.N.T and Neck Specialist
Ex-Registrar E.N.T. Hospital, Bombay

CLINIC

Gujrati Samaj,
Nai Sadak, Ujjain
☎ 2561981
Time Mor: 11 to 2.00

Jai Medical Centre (Near
Vasavda petrol pump)
Ghantaghar, Freegunj, Ujjain
☎ 2514884
Time:eve. 6 to 8.30

SUNDAY HOLIDAY

.....**Specialist**.....

• Nose and sinus endoscopy • Microlaryngeal Surgery • Microear Surgery (Trained from Germany, France and Switzerland) •Plastic Surgery of the Nose (rhinoplasty)

Regarding Duonase

Using this product for last so many days. This is ideal, first line agent for the patient. The combination is adequate to deal with all type of allergy.

- Acts on both phases (early as well as late phase of allergy i.e. inhibit)

- Antagonises the H1 receptor activity with few side effect.

- Acts on multiple symptoms.

- The systemic bioavailability is less so can be used for a longer period without side effect.

Tough to allergy safe to Nose

Confidential

डॉ. प्रसाद र. जवळेकर एम. एस. (ई. एन. टी.)

रजि. नं ०७१८८२
कृष्णा जनरल हॉस्पिटल
गव्हाणे बिल्डींग, पी. सी. एम. टी. चौक, भोसरी,
पुणे ४११०३९. ☎ २७१२९५१६
वेळ : संध्या. ५.०० ते ८-०० वा.

रविवार बंद

धन्वंतरी कान, नाक, घसा हॉस्पि
ओतूर रोड, नारायणगाव
ता. जुन्नर, जि. पुणे, ४१०
☎ ०२१३२ –(हॉस्पि.) २४४०६६,

Date. 27·8·05

I have prescribed "Duonase Nasal Spray for 258 patients Since Aug 2004 to Aug 2005. And I found that Duonase Nasal Spray very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis." Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both in "Duonase Nasal Spray."

So I hereby strongly recommend Duonase Nasal Spray for allergic rhinitis.

[signature]

DR. PRASAD JAWALEKAR M.S (E.N.T)

Reg.no.071882
Krishna General Hospital
Gavhane building, P.C.M.T Chowk,
Bhosari,Pune 411039. ☎ 27129516
Time: eve. 5-00 to 8-00 SUNDAY CLOSED

E.N.T Specialist
Dhanvantari E.N.T.Hospital
Khodad Road, Narayangaon,
Taluka Junnar, Dist. Pune 410504
☎02132-(Hosp.)244766 (R)243969

I have prescribed "Duonase Nasal spray" for 258 patients since Aug 2004 to Aug 2005. And I found that Duonase Nasal Spray very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis", Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both i.e. "Duonase Nasal Spray".

So I hereby strongly recommend Duonase Nasal Spray for allergic rhinitis.

Exhibit B4

Confidential

No: 25409

Dr. Manish Munjal

M.B.B.S., M.S. Diplomate of National Board (ENT), M.N.A.M.S.
D.H.A., D.N.D., D.N.A., D.T.M., DM.S.

EAR - NOSE - THROAT AND HEAD-NECK SURGEON

Ph.: 2300182
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Consultant Otorhinolaryngology & Head-Neck Services
Dayanand Medical College & Hospital, Ludhiana
Formerly Consultant Christian Medical College
and Brown Hospital, Ludhiana.

Clinic-cum-Residence
52-C, Udham Singh Nagar,
Adj. P.A.U. Gate No.4,
Next to Lions Bhawan, Ludhiana

Rx

I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used beclomethasone, budesonide, Azelastine, fluticasone, mometasone, with oral antihistaminics down the line till date.

The present combination spray of a weak (non sedating component) Azelastine and fluticasone (steroidal component) is comp by itself in my patients of chronic simple rhinitis, following nasal & sinus polyposis surgery and those unwilling for surgery or unfit for surgery.

There is a response noted within a week in a few patients but the maximum

Ao. / Pr. / Ro / Lo / Rin. / Web. / Opp. / Jill.

Asso. Aid.: / Under Treatment of: / Cross Consult.:

N. Joshi / Munjal / [signatures]

number of patients responsed very well after three weeks of therapy.

Recurrences of polyposis after functional endoscopic sinus surgery is markedly reduced. Eye itching, crusting and nasal bleed are noted with earlier preparations is not noted to that much extent.

Of course caution/avoidance in diabetic and hypertensive patients is required for fear of worsening or inducing a fungal pathology. (Though have not found much literature on this issue on the net)

The combination therapy (Dexpanthenol) is gradually tapered off by me in two to three months time.

Occasionally, usage is not advised. The entire bottle must be finished for having the best of the results.

Hoping the future is bright for this combination and no one aligns up to some contraindication or side effect of

DR. MANISH MUNJAL

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The combination Therapy (DUONASE) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised. The entire bottle must be finished for having the best of results.

Hoping the future is bright for this combination and no one digs up some contra indication or side effect of this indication.

Exhibit B5

VATS E.N.T. CENTRE

(दिल्ली सरकार द्वारा पंजीकृत)

698/5, Yamuna Vihar Road, (Road No. 66), Maujpur, Delhi-110053

Ph. : 229111 / 22916 / 22911

डॉ० सुरेश वत्स

एम.बी.बी.एस., एम.एस.(ई.एन.टी.)

कान, नाक व गला रोग विशेषज्ञ एवं सर्जन

समय : सुबह 10 से 1 तक शाम 6 से 9 तक

Reimbursible Yes/No. S. No. .... (रविवार अवकाश)

Dr. Suresh Vats

M.B.B.S., M.S. (ENT)
CONSULTANT EAR, NOSE & THROAT SURGEON
Formerly ENT Surgeon
ST. STEPHEN'S HOSPITAL
LNJP & GB PANT HOSPITAL

Age & Sex .... Resi. .... Date .... AM

Name ....

श्रवण शक्ति जाँच Audiometory एवं Speech Therapy
रवि, बुध, शुक्र सुबह 10 से 1 व मंगल शाम 7 से 9 बजे
P.T. Audiogram/Hearing Assessment
Aided Audiogram
Hearing Aid Trial
Speech Assessment
Speech Therapy
Caloric Test
Impedance

Hb TLC, DLC, B.T., C.T.
ESR, Mx-Test
Blood Sugar R-F-Pp, Blood Urea
Urine R/F & M/c
Prothrombin time Platelets Count
HBsAg, HIV 1 & II
AEC IgE, Nasal smear for Eosinophils
VDRL, ASLO Titre
T3 T4 TSH
Sputum/smear for AFB
Throat/Nasal/Ear/Swab C & S
Blood - ova & cyst
FNAC

X-Ray Mastoids - Lat. Oblique(Bil) Towns
X-Ray PNS - Waters
X-Ray Naso-Pharynx-soft Tissue (Lateral)
X-Ray Neck soft Tissue - Lateral
X-Ray cervical Spine - Lat. & A.P.
X-Ray - Styloid Process (Bi-Lateral)
X-Ray Occlusal view for of mouth
X-Ray - Submandibular region - Lat. Rt. - Lt
X-Ray - Internal Auditory Meatus
X-Ray T.M. Joint Lat. Open & closed Jaw
X-Ray - Nasal Bones - Lateral
X-Ray Skull - AP - Lateral
X-Ray - Chest P.A. View
Barium Swallow
C.T. Scan - PNS - Coronal 3 mm cuts
C.T. Scan - Temporal bones
C.T. Scan - Neck / Head
E.C.G.

R L

Rinne's
Weber's

I/L Exa.:

Right Left

Duonase nasal spray
is unique & distinct from
others available nasal spr
due to its combined anti
allergic & antiinflammatory
properties. It is an excel
product, effective in all
patients c Allergic
Rhinitis with or w/o
concomitant Bronchia

Allergy: Worth Trying. Easy to use in certain patients who oral antihistamine may be harmful

17/8/08

Dr. SUMESH VATS
M.S. (ENT)
Sr. CONSULTANT EAR, NOSE & THROAT SURGEON
Reg. No. MCI-2102, DMC-1712
698/5, Road No. 6a, Mangolpuri, Delhi-53

[redacted]

Dr. SURESH VATS

Duonase Nasal spray is unique & distinct from other available nasal sprays due to it combined Anti-allergic & anti-inflammatory properties. It is an excellent product, effective in majority of patients with allergic Rhinitis with or without concomitant Bronchial Allergy. Worth Trying. Safe to use in certain patients where oral antihistamine may be harmful.

Exhibit B6

डॉ. बी. बी. माथुर
एम.डी.

वरिष्ठ विशेषज्ञ एवं एसोसियट प्रोफेसर
चेस्ट एवं टी.बी. विभाग
सरदार पटेल मेडिकल कॉलेज, बीकानेर
RMC No. 7458

Dr. B. B. Mathur
M.D.

Senior Consultant & Associate Professor
Chest & T.B., Hospital
S.P. Medical College, BIKANER
✆ Hos. :0151-2226333, Res.0151-2528789

Ref No.

Date 17/8/05

1) Nonase Nasal Spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients. It take care symptoms due to rapid onset of action and long lasting relief due to anti-inflammatory action.

डॉ. बी. बी. माथुर
एसोसियट प्रोफेसर
सी. बी. एंड टेरस चिकित्सा
सरदार पटेल मेडिकल कॉलेज
बीकानेर (राज.)

Dr. B.B. MATHUR

Duonase Nasal spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients as it take care symptoms due to rapid onset of action and long lasting relief due to anti-inflamattory action.

Exhibit C

Cipla

Therapeutic Index

Nasal Preparations

Duonase Nasal Spray

Azelastine hydrochloride & Fluticasone propionate

Each spray delivers
Azelastine hydrochloride BP ..... 140 mcg
Fluticasone propionate BP ..... 50 mcg

Composition
Fluticasone propionate BP ..... 0.0357% w/v
Azelastine Hydrochloride BP ..... 0.10% w/v
Benzalkonium Chloride NF ..... 0.01% w/v
(as preservative)
Phenyl Ethyl alcohol USP ..... 025% v/v
(as preservative)

Description
Duonase is an antihistamine-corticosteroid combination available as a metered spray formulation for intranasal administration. It contains azelastine hydrochloride, which is a s generation H 1 receptor antagonist with potent topical activity and fluticasone propionate, synthetic corticosteroid with anti-inflammatory properties.

Pharmacology
As Duonase is a combination of Azelastine and Fluticasone; the pharmacological properti both the molecules are given separately.

Pharmacology of Azelastine Hydrochloride
Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H 1 -receptor ant activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H 1 -receptor antagonist activity.

Pharmacokinetics and Metabolism
After intranasal administration, the systemic bioavailability of azelastine hydrochloride is approximately 40%. Maximum plasma concentrations (Cmax) are achieved in 2-3 hours. I on intravenous and oral administration, the elimination half-life, steady-state volume of distribution, and plasma clearance are 22 hours, 14.5 L/kg, and 0.5 L/h/kg, respectively. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excretec feces with less than 10% as unchanged azelastine. Azelastine is oxidatively metabolized principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system specific P450 isoforms responsible for the biotransformation of azelastine have not been identified; however, clinical interaction studies with the known CYP3A4 inhibitor erythromy failed to demonstrate a pharmacokinetic interaction. In a multiple-dose, steady-state drug interaction study in normal volunteers, cimetidine (400 mg twice daily), a nonspecific P45(inhibitor, raised orally administered mean azelastine (4 mg twice daily) concentrations by approximately 65%.

The major active metabolite, desmethylazelastine, was not measurable (below assay limit single-dose intranasal administration of azelastine hydrochloride. After intranasal dosing c azelastine hydrochloride to steady-state, plasma concentrations of desmethylazelastine r

from 20-50% of azelastine concentrations. When azelastine hydrochloride is administerec desmethylazelastine has an elimination half-life of 54 hours. Limited data indicate that the metabolite profile is similar when azelastine hydrochloride is administered via the intranas oral route.

Pharmacology of Fluticasone Propionate
Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory a

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to natural hormone. However, the clinical significance of these findings in relation to the low levels is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symp not known. Corticosteroids have been shown to have a wide range of effects on multiple types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mo (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Pharmacokinetics:
Absorption: Fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic for 3 weeks, fluticasone propionate plasma concentrations were above the level of detecti pg/mL) only when recommended doses were exceeded and then only in occasional samp low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted fro plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circ radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, the initial disposition phase for flut propionate was rapid and consistent with its high lipid solubility and tissue binding. The vc distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% obvious concentration relationship. Fluticasone propionate is weakly and reversibly bounc erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propio not significantly bound to human transcortin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1,0 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circula metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propio which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of hum cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolite detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexpor kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excre the feces as parent drug and metabolites.

Indications
Duonase is indicated for the management of symptoms of allergic rhinitis once the neec antihistamine and corticosteroid has been established. It is recommended to treat **mode severe persistent symptoms** in adults above 12 years. For children above 5 years **Duonase** is recommended for **severe symptoms** of allergic rhinitis. **Duonase** can used for treating non-allergic vasomotor rhinitis in adults and children 12 years of age anc

Dosage And Method of Administration
Adults and children 5 years and older: 1 spray/nostril twice daily

The recommended dosage should not be exceeded. Not recommended for use in childrer 5 years.

Contact Us

Essential Update

News Update
HIV/AIDS Update
Respiratory Update
Cardiology Update
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Contraindications
Duonase is contraindicated in patients with or known hypersensitivity to azelastine hydroc or fluticasone propionate or any of the components of the preparation.

Warnings and Precautions

- Concurrent use of this combination with alcohol or other CNS depressants or othe antihistamines should be avoided as additional reductions in alertness and additio impairment of CNS performance may occur due to azelastine.
- The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. Some patients may experience syr of withdrawal e.g. joint and/or muscular pain, lassitude and depression.
- The concomitant use of an intranasal corticosteroid with other corticosteroids coul increase the risk of signs or symptoms of hypercorticism and/ or suppression of th axis. Therefore the combination should be used cautiously in patients with other pathological conditions requiring steroids.
- Intranasal corticosteroids may cause a reduction in growth velocity when administ higher dose. The recommended dosage of **Duonase** should not be exceeded.
- Special care is needed in patients with lung tuberculosis and fungal and viral infec Children who are on immunosuppressant drugs are more susceptible to infections healthy children. Chicken pox and measles for example can have a more serious a fatal course in children on immunosuppressant corticosteroids.
- During long term therapy, monitoring of hematological and adrenal function is adv
- In clinical studies with intranasal fluticasone propionate, the development of localiz infections of the nose and the pharynx with *Candida albicans* has been seen rarel such an infection develops, it may require treatment with appropriate local therapy discontinuation of the treatment with **Duonase** is advised

Drug Interactions
The use of **Duonase** in patients taking concurrent drugs, which are potent inhibitors of tl cytochrome 450 3A4 system eg. Ketoconazole and protease inhibitors such as ritonavir m associated with increased systemic exposure of fluticasone.

Pregnancy
The combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
It is not known whether azelastine hydrochloride or fluticasone propionate is excreted in h milk. Hence, caution should be exercised while prescribing this combination to nursing m

Undesirable Effects
The most likely side effects with this combination are headache, somnolence, pharyngitis, epistaxis, nasal burning/irritation, nausea, vomiting, cough, taste disturbance. The combir may produce a bitter taste, which may lead to occasional nausea. Bitter taste disappears sometime.

Shelf Life
2 years

Storage and Handling Instructions
Store below 30 ^{0} C.
Do not refrigerate.
Protect from direct sunlight.

Packaging Information
Duonase Nasal Spray
Sales pack contains 70 metered doses

Last Updated: M

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Sr. No	TEST		FLUTICASONE PROPIONATE AQUEOUS NASAL SPRAY
1	ASSAY	Preparation of Mobile Phase	Acetonitrile, Ammonium phosphate buffer pH 3.5 and methanol in the ratio of 15:35:50.
		Column	A stainless steel column 15 cm X 4.6 mm internal diameter packed with octadecylsilyl silica gel for chromatography (5 µm)
		Flow rate	About 1.5 ml/min
		Detection wavelength	239nm
		Column oven temperature	40°C
		Retention time	About 6.5minutes
		Run time	10 minutes
		Injection volume	100µl of each solution
		Diluent	Mobile Phase
		Standard preparation	1ppm Fluticasone propionate
		Sample preparation	1ppm Fluticasone propionate
2	RELATED SUBSTANCES	Preparation of Mobile Phase A	Acetonitrile and methanol (97: 3)
		Preparation of Mobile Phase B	Water, methanol and Orthophosphoric acid (97: 3: 0.1)
		Column	15 cm X 4.6mm column that contains 5µ packing L1 with guard column 50mm X 4.6mm, 5µ packing L1
		Flow rate	1.5 ml/min
		Detection wavelength	239nm
		Column oven temperature	40°C
		Run time	70 minutes
		Injection volume	100µl
		Diluent	Distilled Water: Acetonitrile (50:50)
		Standard preparation	100ppm Fluticasone propionate
		Reference preparation	1ppm Fluticasone propionate
		Sample preparation	100ppm Fluticasone propionate
		Impurities monitored	Fluticasone acid propionate
			Fluticasone acetate
			S-methyl Fluticasone
			Chloro Fluticasone
			Iodo Fluticasone

Sr. No	TEST		AZELASTINE HYDROCHLORIDE NASAL SPRAY
1	ASSAY	Preparation of Mobile Phase	Methanol, Ammonium phosphate Buffer and Acetonitrile in the ratio of (450:400:150), 1ml of Triethylamine, pH = 5.0
		Column	Octadecylsilyl C18, 25 cm X 4.6mm, 5µm column
		Flow rate	About 1.2 ml/min
		Detection wavelength	290nm
		Column oven temperature	25°C
		Retention time	About 6.0 minutes
		Run time	10.0 minutes
		Injection volume	20µl
		Diluent	Buffer : Acetonitrile: Methanol (350:350:300)
		Standard preparation	50ppm Azelastine HCl
		Sample preparation	50ppm Azelastine HCl
2	RELATED SUBSTANCES	Preparation of Mobile Phase A	Ammonium phosphate buffer, Acetonitrile, Methanol in the ratio of (510:140:350); adjust pH to 5.0 with 1ml of triethylamine
		Preparation of Mobile Phase B	Ammonium phosphate buffer, Acetonitrile, Methanol in the ratio of (300:300:400); adjust pH to 5.0 with 1ml of triethylamine
		Column	15 cm X 4.6mm column that contains 5µ packing L1 with 20mm X 4.0mm, guard of packing L1.
		Flow rate	1.0ml/min
		Detection wavelength	290nm
		Column oven temperature	40°C
		Run time	60 minutes
		Injection volume	50µl of each solution
		Diluent	Buffer : Acetonitrile: Methanol (350:350:300)
		Standard preparation	250ppm Azelastine HCl
		Reference preparation	2.5ppm Azelastine HCl
		Sample preparation	250ppm Azelastine HCl
		Impuritles monitored	N-oxide A
			N-oxide B
			Impurity D

Sr. No	TEST		AZELASTINE HYDROCHLORIDE AND FLUTICASONE PROPIONATE NASAL SPRAY	
1	ASSAY	Preparation of Buffer solution	0.01M Ammonium dihydrogen orthophosphate, pH 3.5 with dilute orthophosphoric acid	
		Preparation of Mobile Phase	Methanol : Buffer solution : Acetonitrile (500 : 350 : 150)	
		Column	C8, 25 cm x 4.6mm, 5µm	
		Flow rate	1.5 ml/min	
		Detection wavelength	239 nm	
		Column oven temperature	40°C	
		Injection volume	20µl	
		Standard preparation	For Azelastine hydrochloride: about 50 ppm For Fluticasone propionate: about 18 ppm	
		Sample preparation	For Azelastine hydrochloride: about 50 ppm For Fluticasone propionate: about 18 ppm	
2	RELATED SUBSTANCES		Azelastine HCl	Fluticasone Propionate
		Preparation of Mobile Phase A	0.01M Ammonium dihydrogen phosphate, pH 3.5 with orthophosphoric acid	Acetonitrile, Methanol and orthophosphoric acid (970 :30:0.5)
		Preparation of Mobile Phase B	Acetonitrile and Methanol (1:1)	Water, Methanol and orthophosphoric acid (970 :30:0.5)
		Column	C18, 25cm x 4.6mm, 5µm	C18, 25cm x 4.6mm, 5µm
		Flow rate	1.0ml/min	1.0ml/min
		Detection wavelength	239nm	239nm
		Column oven temperature	40°C	40°C
		Injection volume	10µl of each solution	20µl of each solution
		Diluent	Methanol	Mobile phase A
		Standard preparation	About 500 ppm Azelastine HCl	About 175 ppm Fluticasone Propionate
		Reference preparation	About 1 ppm Azelastine HCl	About 0.175 ppm Fluticasone Propionate
		Sample preparation	About 500 ppm Azelastine HCl	About 178.5 ppm Fluticasone Propionate
		Impurities monitored	1-methyl-4-2-(benzolyhydrazino) azepan	Impurity A - 6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo-17-(propanoyloxy) androsta-1,4-diene-17β-carboxylic acid
				Impurity B - [[6α,9-difluoro-11β-hydroxy-16α-

	yl]carbonyl]sulphenic acid
	Impurity C - 6α,9-difluoro-17-[[(fluoromethyl) sulphanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl acetate
	Impurity D - 6α,9-difluoro-17-[(methylsulphanyl)carbonyl]-11β-hydroxy-16α-methyl-3-oxo androsta-1,4-dien-17α-yl propanoate
	Impurity E - 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl] -11β-hydroxy-16α-methyl-3-oxoandrost-4-en-17α-yl propanoate
	Impurity F - 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl] -16α-methyl-3,11-dioxoandrosta-1,4-dien-17α-yl propanoate
	Impurity G - 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl] -11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylate
	Impurity H - 17,17'-(disulphanediyldicarbonyl) bis(6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl) dipropanoate
	Impurity I - 7,17'-(trisulphanediyl dicarbonyl)bis(6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo androsta-1,4-dien-17α-yl) dipropanoate

Sr. No	TEST		BUDESONIDE NASAL SPRAY
1	ASSAY	Preparation of Mobile Phase	Acetonitrile : Distilled water (65 : 35)
		Column	C18, 25 cm x 4.6mm, 5µm
		Flow rate	2.0 ml/min
		Detection wavelength	242 nm
		Column oven temperature	25°C
		Run time	5 minutes
		Injection volume	20µl
		Diluent	Mobile phase
		Standard preparation	20 ppm
		Sample preparation	20 ppm
2	RELATED SUBSTANCES	Preparation of Mobile Phase	0.025M Sodium phosphate Buffer pH 3.2 and Acetonitrile in the ratio of (720 :280)
		Column	Octadecylsilicagel C18, 25cm x 4.6, 5µm
		Flow rate	1.5ml/min
		Detection wavelength	240nm
		Column oven temperature	25°C
		Run time	60 minutes
		Injection volume	20µl of each solution
		Diluent	Acetonitrile and mobile phase
		Standard preparation	320ppm
		Reference preparation	3.2ppm
		Sample preparation	320ppm
		Impurities monitored	Desonide (Imp F as per Ph Eur)
			21 - Dehydrobudesonide epimer I (Imp D as per USP)
			21 - Dehydrobudesonide epimer II (Imp D as per USP)

Sr. No	TEST		AZELASTINE + BUDESONIDE NASAL SPRAY	
1	ASSAY	Prepration of Mobile Phase B	0.01M Ammonium phosphate Buffer,Acetonitrile and methanol (300:300: 400)	
		Column:	C18, 25 cm x 4.6mm column that contains 5µ packing	
		Flow rate:	1.0 ml/min	
		Detection wavelength:	242nm	
		Column oven temperature:	45°C	
		Run time:	9 minutes	
		Injection volume:	20µl	
		Diluent	Buffer,Acetonitrile and methanol (350:350: 300)	
		Standard preparation	20ppm Azelastine	10ppm Budesonide
		Sample preparation	20ppm Azelastine	9.3ppm Budesonide
2	RELATED SUBSTANCES	Prepration of Mobile Phase A	Buffer,Acetonitrile and methanol (51:14: 35)+1 ml of TEA /litre----- pH 5.0 with Orthophosphoric acid	
		Prepration of Mobile Phase B	Buffer,Acetonitrile and methanol (30:30: 40)+1 ml of TEA /litre----- pH 5.0 with Orthophosphoric acid	
		Buffer	1.15 gm Ammonium dihydrogen ortho phosphate--------->1000 ml Distilled water	
		Column:	C18, 15 cm X 4.6mm column that contains 5µ packing with C18 guard column	
		Flow rate:	1.0 ml/min	
		Detection wavelength:	254nm	
		Column oven temperature:	40°C	
		Run time:	70 minutes	
		Injection volume:	50µl	
		Diluent	Buffer,Acetonitrile and methanol (35:35: 30)	
		Standard preparation	250ppm Azelastine	100ppm Budesonide
		Reference preparation	2.5ppm Azelastine	1ppm Budesonide
		Sample preparation	250ppm Azelastine	117ppm Budesonide
		Impurities monitored	N-oxide A Impurity of Azelastine	
			N-oxide B Impurity of Azelastine	
			Impurity D of Azelastine	
			Impurity D of Budesonide (as per Ph Eur.)	
			Impurity A of Budesonide (as per Ph Eur.)	
			Impurity B of Budesonide (as per Ph Eur.)	
			Impurity F of Budesonide (as per Ph Eur.)	
			Impurity E of Budesonide (as per Ph Eur.)	
			Impurity G of Budesonide (as per Ph Eur.)	